REMARKS

The Applicant has advised that he has no further patents or applications that should be drawn to the examiner's attention beyond those already discussed.

Turning now to the obviousness type double patenting rejection of claims 3 and 10 over US 6,627,659, as noted by the examiner, this claims

> A method of decreasing the effect of oxidative stress in a patient, having renal disease undergoing chronic hemodialysis comprising administrating intravenously, during dialysis, N-acetylcysteine or a pharmaceutically acceptable salt thereof in an amount effective to decrease the effect of oxidative stress in said patient.

The examiner notes that at page 5 of the present application it is stated that the applicant had "recently reviewed the therapeutic uses of cysteine pro-drugs such as N-acetyl cysteine ..." Reliance on this passage, however, is impermissible viewing of the present invention through the eyes of the inventor, not one of ordinary skill in the art. Nothing in the cited art points to acetylcysteine as being known as a prodrug for cysteine. As noted at page 3 line 4 of the present application just prior to the filing of the present application, the inventor had published a review of the therapeutic uses of cysteine pro-drugs such as N-acetyl cysteine and other derivatives. One aim of the review was to report all the attempts to modify the chemical structure of cysteine in order to overcome the pharmacokinetic and metabolic limits of cysteine *per se*. In particular US Patent 6627659 has two important differences with respect to the present invention. The use of an intravenous route of administration is more expensive, less safe and more troublesome than oral administration as required by the present claims in cases where, as here, a long term infusion would be required to infuse a large volume of a dilute solution of N-acetyl cysteine against the positive pressure of blood flow. Moreover, N-acetylcysteine rather than cysteine itself was used, even though the latter is natural and cheaper. It is likely that this is because the inventors were looking to the properties of N-acetylcysteine itself to effect a direct pharmacological effect rather than looking at it as a prodrug for cysteine..

In fact, those skilled in the art did not regard acteylcysteine administered orally as required by the present claims as a pro drug for cysteine. Submitted herewith is a paper by Soldini et al Eur J Clin. Phharmacol (2005) 60 859-864 which was submitted for publication between the priority date and filing date of the present application and so gives a good indication of thinking at the relevant time. This article shows that the authors regarded N-acetyl cysteine as acting in its own right not as a prodrug. A similar conclusion can be drawn from Parmentier et al Eur Resir J 2000 923 - 939, a copy of which is also enclosed.

It is therefore submitted that there is no basis for concluding that it was obvious to replace the Nacteyl cysteine used in the invention claimed in US 6627659 by cysteine as claimed in claims 3 and 10 of the present application.

Turning now to the rejection under 35 USC 103, this again relies on the assumption that what applies to N-acetyl cysteine would also apply to cysteine. As noted above, there is no rational basis for this. In essence Locatelli confirms what is set out in the introductory portion of the present application, namely that oxidative stress has been observed in patients suffering from kidney failure. The only reference to any cysteine derivative seems to be in the conclusions on the first page where it is suggested that tests with antioxidants need to be carried out to investigate the role of oxidative stress in patient morbidity and mortality. Antioxidants suggested for testing are vitamin E, vitamin C, N-acetyl cysteine and L-arginine. N-acetyl cysteine is well known as an antioxidant. Although cysteine has antioxidant properties, there is no reason to think that it could be substituted for N-acetyl cysteine in any particular specific situation. The fact that the alternatives suggested by Locatelli are vitamins E and C and L-arginine indicate that the authors of this paper did not see cysteine itself as a suitable material for its purpose. It is true that Droge mentions a number of cysteine derivatives (including N-acetyl cysteine) as possibly serving as " a cysteine source" because they are transportable across cell membranes. However, this does not means that cysteine and N-acetyl cysteine are interchangeable. Droge is seeking to insert cysteine into liposome

lumens so that it can result in an increase of the thiol level in blood plasma. Nothing in this suggests that cysteine itself should be used as set out in the present claims.

A person skilled in nephrology would have not been motivated by Locatelli to use a different chemical entity (cysteine instead of NAC) [and a different administration route. The selection of NAC was of course intentional for exploiting the specific properties of NAC as such, not as a pro-drug.. Locatelli did not therefore consider NAC as a mere pro-drug of cysteine, as confirmed inter alia by the other papers submitted herewith.

Droge does not provide a complementary teaching: Droge in fact always refers to a "cysteine source" rather than to "cysteine". The concrete data reported in the specification of Droge always refer to the oral administration of NAC (see column 5, lines 47, 52 and 66. See also column 3, line 40). The definition of "cysteine source" is clearly referring to a derivative of cysteine, as reported on column 2, lines 29-36: "Thus, normally cysteine derivatives will be employed ... ". Droge does not even accordingly teach the oral administration of cysteine as such, but of a derivative thereof.

Oral treatment with cysteine itself could not accordingly be derived from the combination of Locatelli and Droge.

It should moreover be noted that a skilled in the art aware of the fact that cysteine is already naturally present in higher concentrations serum of patients undergoing hemodialysis (see enclosed abstract), would have no motivation to administer additional cysteine.

It is therefore submitted that the requirements of 35 USC 103 have been complied with and that this application should be allowed.

Respectfully submitted,

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